CLINICAL RESEARCH

Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913

B LARSSON, K SVÄRDSUDD, L WELIN, L WILHELMSEN, P BJÖRNTORP, G TIBBLIN

Abstract

In a prospective study of risk factors for ischaemic heart disease 792 54 year old men selected by year of birth (1913) and residence in Gothenburg agreed to attend for questioning and a battery of anthropometric and other measurements in 1967. Thirteen years later these baseline findings were reviewed in relation to the numbers of men who had subsequently suffered a stroke, ischaemic heart disease, or death from all causes.

Neither quintiles nor deciles of initial indices of obesity (body mass index, sum of three skinfold thickness measurements, waist or hip circumference) showed a significant correlation with any of the three end points studied. Statistically significant associations were, however, found between the waist to hip circumference ratio and the occurrence of stroke ($p=0.002$) and ischaemic heart disease ($p=0.04$). When the confounding effect of body mass index or the sum of three skinfold thicknesses was accounted for the waist to hip circumference ratio was significantly associated with all three end points. This ratio, however, was not an independent long term predictor of these end points when smoking, systolic blood pressure, and serum cholesterol concentration were taken into account.

These results indicate that in middle aged men the distribution of fat deposits may be a better predictor of cardiovascular disease and death than the degree of adiposity.

Section of Preventive Medicine, Department of Medicine I, Sahlgrenska Hospital, Gothenburg, Sweden

B LARSSON, MD, PHD, associate professor

P BJÖRNTORP, MD, PHD, professor

Östra Hospital, University of Gothenburg, Sweden

K SVÄRSUDD, MD, PHD, associate professor

L WELIN, MD, PHD, associate professor

L WILHELMSEN, MD, PHD, associate professor

Department of Family Medicine, University of Uppsala, Sweden

G TIBBLIN, MD, PHD, professor

Correspondence to: Professor B Larsson, Department of Medicine I, Sahlgrenska Hospital, 413 45 Göteborg, Sweden.

Introduction

Severely overweight people—especially the young—have an increased risk of dying or of contracting a serious illness.[1] The evidence for less overweight people is more conflicting.[2-6] The effect of excess weight on cardiovascular disease and mortality is delayed[1 7 8] and therefore often not evident in short term studies. Health hazards of overweight are difficult to define in prospective studies of the general population, since unless these comprise a very large number of people they are likely to include few excessively overweight subjects. These problems were evident in a study of the health consequences of obesity in a cohort of men born in 1913.[9]

In an attempt to see whether various distributions of adipose tissue might be associated with an increased risk of cardiovascular disease or death we studied the relation between baseline measurements of abdominal adipose tissue distribution (waist to hip circumference ratio) and commonly used indices of obesity and the incidences of stroke, ischaemic heart disease, and death from all causes over the next 13 years.

Subjects and methods

The study population comprised men living in Gothenburg who were born in 1913 and whose date of birth was divisible by three—that is, the third, sixth, ninth days, and so on, of each month. Of those approached, 855 (88%) agreed to be examined in 1963. The population—participants and non-participants—have been described elsewhere.[10 11] The 855 participants in 1963 were invited to attend for re-examination in 1967 (aged 54), and 792 (94%) of those still alive accepted. As part of this re-examination a large number of anthropometric measurements were made, which served as baseline values for the present analysis.

ANTHROPOMETRIC STUDIES

Body weight was measured to the nearest 0·1 kg with a balance scale, the men wearing underpants only. Height was measured to the nearest centimetre. *Body mass index* was calculated as weight (kg)/height (m)^2. *Skinfold thicknesses* (triceps, subscapular, and parathoracic—that is, midway between the axilla and iliac crest) were measured with Harpenden's calipers and recorded to the nearest 0·1 mm. *The (three) skinfold thicknesses* were then summed. *Waist circumference* was measured to the nearest centimetre at the level of the umbilicus with the subject standing and breathing normally. *Hip circumference* was measured to the nearest centimetre at the level of the iliac crest. All anthropometric measurements were performed by a single observer.

In an attempt to determine the predictive power of abdominal adipose tissue distribution the waist to hip circumference ratio was calculated. The correlation between the two circumferences was high ($r=0·86$; $p<0·001$). The ratio was approximately normally distributed (fig 1), as were the other measures of obesity used in the study.

Blood pressure was recorded sitting after a five minute interview; pressure was taken to the nearest 5 mm Hg using a cuff with a rubber bag measuring 12 × 23 cm. The examination was conducted between 2 and 3 pm. *Blood samples* for determination of serum cholesterol concentration[12] were drawn after a four hour fast. *Smoking habits* were recorded as never smoked, stopped smoking (ex-smoker), smoking 1-14 g tobacco daily, smoking 15-24 g/day, or smoking 25 g or more daily.

FOLLOW UP AND END POINTS

The men were followed up by re-examination in 1973-4 and 1980-1. Further information was obtained by postal questionnaires and by scrutiny of death certificates, periodic review of the population register—which records births, deaths, etc and by law must be kept up to date—and from myocardial infarction and stroke registers covering the city of Gothenburg.[13 14] The follow up rate was 100%.

The combined incidence of clinically recognised myocardial infarction and death from myocardial infarction or other ischaemic heart disease was used as the end point cardiovascular disease. The clinical criteria of myocardial infarction were those adopted by the Swedish Society of Cardiology: central chest pain, shock, or, syncope suggesting myocardial infarction together with typical serum transaminase activities or a pathological Q wave or localised ST changes in the electrocardiogram. Death from myocardial infarction or ischaemic heart disease was based on evidence at necropsy (carried out in 82% of deaths) or available clinical data. A complete description of the definition has been published.[13]

The criterion for stroke was admission to hospital with a diagnosis of stroke or the finding of fresh cerebral thrombosis or haemorrhage at necropsy.

STATISTICAL METHODS

Besides conventional Student's t and χ^2 tests we used Pitman's permutation test, a non-parametric test for correlation and multivariate analysis.[15] The isotonic regression technique was used for construction of the regression surfaces. By contrast with the linear and logistic regression technique, the isotonic model does not require any specific functional form for the dependent variable. A p value of $<0·05$ was taken as statistically significant. Levels of significance were denoted as: *$0·01<p<0·05$; **$0·001<p<0·01$; ***$p<0·001$.

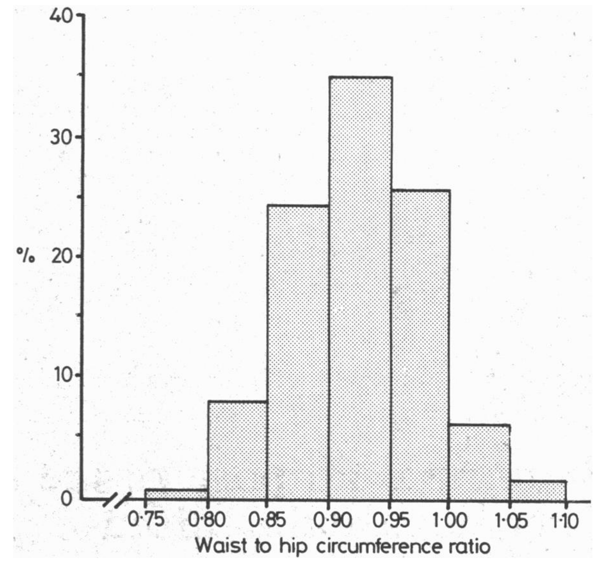

FIG 1—Percentage distribution of waist to hip circumference ratios at baseline in 54 year old men.

Results

During the 13 years of follow up 33 cases of stroke, 91 cases of ischaemic heart disease, and 109 deaths from all causes were recorded among men without previous evidence of myocardial infarction or stroke. Table I gives the mean values of selected variables of the total cohort at baseline and also the characteristics of subjects who did and did not suffer stroke, ischaemic heart disease, or death. Of the indices of obesity used, only the waist to hip circumference ratio differed significantly between cases and non-cases. Subjects with stroke and ischaemic heart disease had significantly higher waist to hip circumference ratios than non-cases. Systolic blood pressure was a risk factor for stroke but serum cholesterol concentration and smoking were not. Systolic blood pressure and smoking were risk factors for death from all causes but serum cholesterol concentration was not. Traditional risk factors for ischaemic heart disease (blood pressure, serum cholesterol concentration, and smoking) were significantly correlated with the incidence of the disease.

TABLE I—*Comparison of selected variables among men aged 54 at baseline who subsequently suffered (cases) or did not suffer (rest) stroke, ischaemic heart disease, or death from all causes. Except where stated otherwise, values are means (SD in parentheses)*

	Stroke		Ischaemic heart disease		Death		Total
	Cases	Rest	Cases	Rest	Cases	Rest	
Body mass index (kg/m²)	25·3 (3·3)	25·0 (3·2)	25·0 (3·4)	25·0 (3·1)	25·0 (3·6)	24·9 (3·1)	25·0 (3·2)
Sum of skinfold thicknesses (mm)	47·9 (18·1)	45·9 (16·9)	44·6 (15·8)	46·2 (17·1)	44·6 (17·1)	46·3 (16·9)	46·1 (17·1)
Waist circumference (cm)	89·3 (8·8)	86·8 (9·4)	87·4 (9·5)	86·9 (9·5)	87·5 (10·0)	86·8 (9·2)	86·0 (9·4)
Hip circumference (cm)	93·2 (6·7)	93·7 (7·1)	93·1 (7·6)	93·8 (7·0)	93·5 (7·3)	93·7 (7·1)	93·7 (7·2)
Waist to hip circumference ratio	0·958 (0·051)***	0·925 (0·053)	0·938 (0·051)*	0·925 (0·054)	0·935 (0·053)	0·925 (0·053)	0·927 (0·054)
Systolic blood pressure (mm Hg)	152·9 (26·0)*	143·5 (20·9)	152·2 (25·5)***	142·8 (20·3)	150·9 (25·6)***	142·8 (20·1)	143·8 (21·1)
Serum cholesterol (mmol/l)	7·20 (1·42)	7·00 (1·18)	7·47 (1·28)***	6·96 (1·17)	6·71 (1·34)	6·98 (1·17)	7·01 (1·19)
Smokers (%)	58·9	51·6	63·3*	49·5	65·8**	49·4	55·1

*$p<0·05$. **$p<0·01$. ***$p<0·001$.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

Repeating the analyses of the indices of obesity versus the risk of stroke, ischaemic heart disease, and death (using a non-parametric correlation test[15]) yielded statistically significant associations for the waist to hip circumference ratio and stroke ($p=0·002$) and ischaemic heart disease ($p=0·04$) but not death ($p=0·053$). Similar results were obtained when the association between waist circumference and these end points was tested in partial correlation analyses with hip circumference kept constant. No significant associations were found for other indices of obesity (body mass index; sum of skinfold thicknesses; specific skinfold thicknesses; ratio of triceps to subscapular skinfold thickness; specific circumferences (waist and hip)).

Figure 2 shows the 13 year incidences of stroke, ischaemic heart disease, and death from all causes by centiles of the waist to hip circumference ratio. The associations tended to be linear for total mortality and ischaemic heart disease but curvilinear for stroke. The risk ratio between the highest quintile and lowest quintile was 1·7 for death, 2·5 for ischaemic heart disease, and 5·9 for stroke. A high waist to hip circumference ratio carried a high risk of stroke,

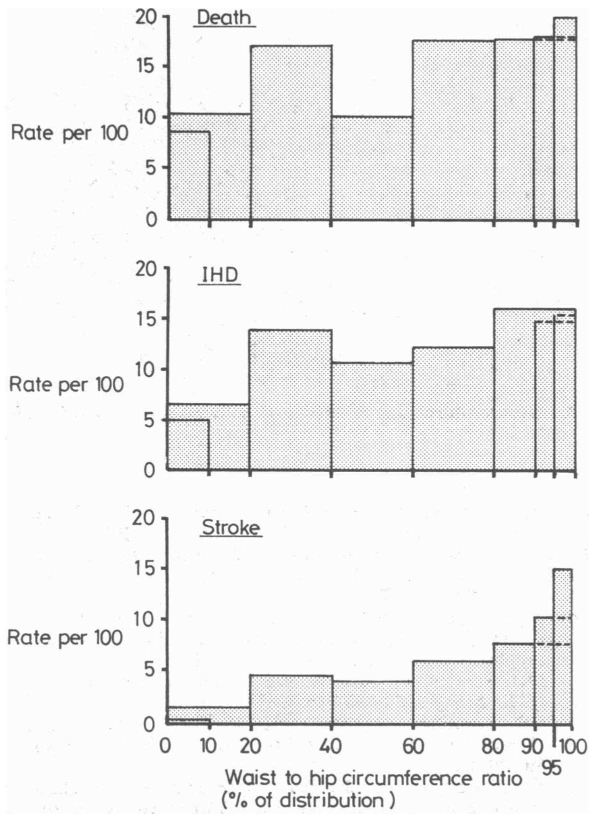

FIG 2—Thirteen year incidences of death from all causes, ischaemic heart disease (IHD), and stroke by waist to hip circumference ratio in men aged 54 at entry.

as indicated by a risk ratio of 11·5 when subjects in the 95th percentile and over were compared with those in the lowest quintile. Among the 10% with the lowest waist to hip circumference ratios not a single man developed stroke.

Table II lists the mean values for systolic blood pressure, diastolic blood pressure, serum cholesterol concentration, smoking, body mass index and sum of the three skinfold thicknesses in quintiles of the waist to hip circumference ratio. For smoking there was no significant association, but for serum cholesterol a positive trend was found ($r=0·08$). Significant positive associations were found between the waist to hip circumference ratio on the one hand and systolic ($r=0·13$) and diastolic ($r=0·24$) blood pressures, body mass index ($r=0·60$), and sum of three skinfold thicknesses ($r=0·53$) on the other. Only the association between the waist to hip circumference ratio and systolic blood pressure remained significant when body mass index or sum of the three skinfold thicknesses was accounted for in partial correlation analyses.

To see if there was an association between the waist to hip circumference ratio and the risk of cardiovascular disease and death when the degree of obesity also was accounted for, a multivariate analysis was performed. For all three end points the correlation was significant when body mass index or the sum of skinfold thicknesses was accounted for.

Figure 3 depicts the combined influence of body mass index and waist to hip circumference ratio on the risks of stroke, ischaemic heart disease, and death using the isotonic regression method. Within a body mass index group the risk of stroke increased with increasing waist to hip circumference ratio. The same was true for the risk of ischaemic heart disease. In that case, however, the lowest risk was found in the group of men with a high body mass index and low waist to hip circumference ratio (5·6%) and the highest risk in men with a low body mass index and high waist to hip circumference ratio (20·8%). A similar trend was found for the risk of death from all causes. Those who had a high body mass index but a low waist to hip circumference ratio had the lowest risk of death (5·3%) and those who had a low body mass index and a high waist to hip circumference ratio the highest risk of death (29·2%).

Adjusting for a possible negative confounding effect of smoking, statistical significance ($p<0·05$) was reached for all the end points and the waist to hip circumference ratio but not for any other index of obesity. The waist to hip circumference ratio, however, was not an independent long term predictor of these end points when systolic blood pressure and serum cholesterol concentration were taken into account.

Discussion

In the general population sample of 54 year old men examined in this study no association was found between risk of cardiovascular disease and death and indices of obesity such as sum of skinfold thicknesses or body mass index during 13 years of follow up. This might seem paradoxical, because several risk factors for cardiovascular disease are associated with obesity—for example, hyperlipidaemia and hypertension.[16]

One of the possible negative confounding factors of the relation between obesity and cardiovascular disease and death is smoking.[16 17] In this population smoking was a strong risk factor for ischaemic heart disease and death. As in many other studies, smokers were leaner than non-smokers. Thus smoking had to be considered.

Another factor is the possible heterogeneity of human obesity—that is, only certain subgroups might be at risk for severe complications. Vague reported a difference in prevalence of various cardiovascular risk factors between obese subjects with adipose tissue located in the upper and lower parts of the body.[18] A recent cross sectional analysis showed the importance of abdominal obesity for these associations. Thus a higher risk of cardiovascular disease was calculated in highly selected obese men and women with abdominal obesity—expressed, for example, as the waist to hip circumference ratio—even when body fat was taken into account.[19] We used a similar classification

TABLE II—*Risk factors for ischaemic heart disease in relation to quintiles of waist to hip circumference ratio. Except where stated otherwise, values are means (SD in parentheses)*

Quintile of waist to hip circumference ratio	Blood pressure (mm Hg)		Serum cholesterol (mmol/l)	Smokers (%)	Body mass index	Sum of skinfold thicknesses
	Systolic	Diastolic				
I	140 (22)	86 (13)	6·83 (1·12)	57·4	22·2 (2·4)	32·3 (11·1)
II	142 (21)	89 (11)	7·01 (1·22)	51·0	23·9 (2·3)	40·5 (12·1)
III	146 (24)	91 (13)	7·02 (1·13)	49·4	25·1 (2·5)	47·3 (15·3)
IV	145 (20)	92 (13)	7·07 (1·15)	53·8	26·0 (2·6)	52·2 (14·8)
V	147 (18)	94 (11)	7·13 (1·32)	47·7	27·7 (3·1)	57·9 (18·5)
All	144 (21)	91 (12)	7·01 (1·19)	55·1	25·0 (3·2)	46·1 (17·1)
p Value	<0·001	<0·001)	NS	NS	<0·001)	<0·001

NS = Not significant.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

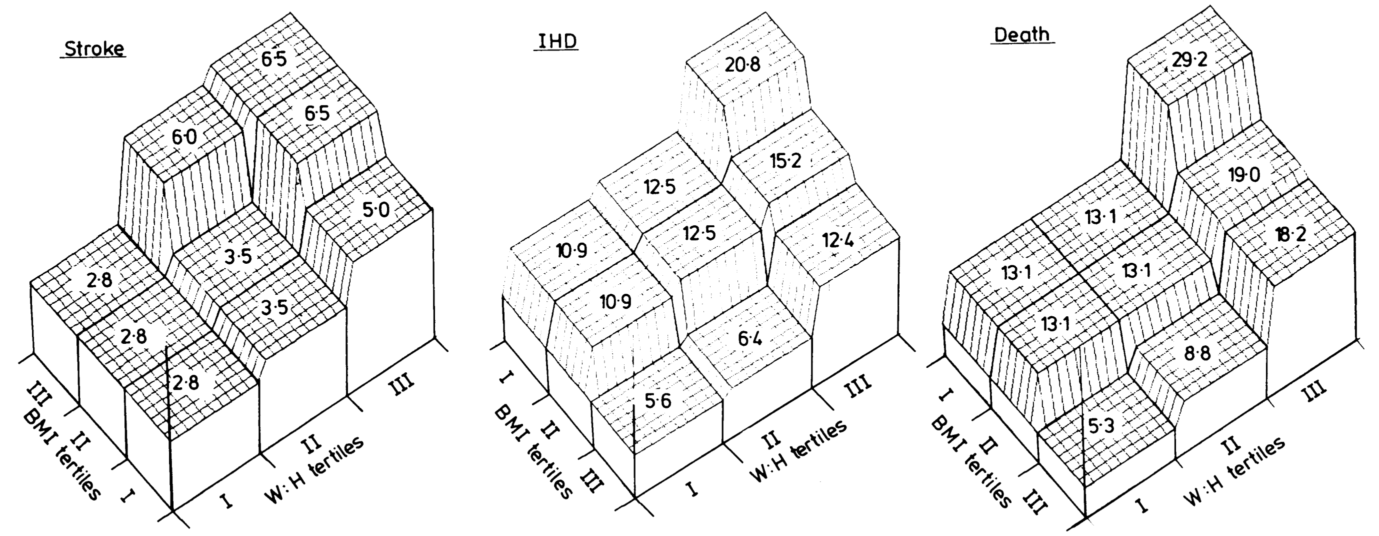

FIG 3—Percentage probabilities of stroke, ischaemic heart disease (IHD), and death from all causes in relation to tertiles of body mass index (BMI) and waist to hip circumference (W:H) ratio. (BMI axes reversed for death and IHD.)

of obesity and consider that the waist to hip circumference ratio is a practical and simple index of the abdominal adipose tissue distribution.

Even though associations with the waist to hip circumference ratio were not significant in multivariate analysis when blood pressure and serum cholesterol concentration were taken into account, the ratio was evidently more closely associated with the risk of cardiovascular disease than were other indices of obesity. A high ratio might be indirectly associated with increased risk, serving only as a marker of some hitherto unknown unfavourable host or environmental factor. Recent work also suggests possible pathophysiological mechanisms for a direct relation between abdominal obesity and cardiovascular risk factors. The intra-abdominal adipocytes are unique because they empty their free fatty acids directly into the portal vein, exposing the liver to high concentrations of free fatty acids. Experimentally induced high portal free fatty acid concentrations inhibit uptake of insulin by the liver (G Strömblad *et al*, paper submitted for publication). This might lead to peripheral hyperinsulinaemia, which in turn might be followed by relative insulin insensitivity and therefore also by a tendency to develop diabetes mellitus. The role of increased insulin concentrations in raised blood pressure has been discussed.[20 21] High portal free fatty acid concentrations cause hypertriglyceridaemia.[22]

Thus there exist pathophysiological mechanisms whereby increased abdominal fat may increase the portal free fatty acid concentration, cause disturbed plasma lipid concentrations as well as hyperinsulinaemia, and possibly also increase blood pressure.

In conclusion, this prospective study of a population sample of middle aged men indicates that abdominal adipose tissue distribution as a predictor of cardiovascular disease and death may be used independently of commonly used indices of the degree of adiposity but not independently of serum cholesterol concentration and blood pressure.

This work was supported by grants from the Swedish Medical Research Council (B84-27X-06276-03), the Swedish National Association against Heart and Chest Diseases, the Göteborg Medical Association, and the Swedish Diabetes Association. We thank Kjell Pennert for the statistical analyses. Part of this paper was presented at the Fourth International Congress on Obesity, New York, 5-7 October 1983.

References

1 Society of Actuaries and Association of Life Insurance Medical Directors. *Build study* 1979. Chicago: Recording and Statistical Corporation, 1980.

2 Keys A. *Seven countries. A multivariate analysis of death and coronary heart disease.* London: Harvard University Press, 1980.

3 Dawber TR. *The Framingham study. The epidemiology of atherosclerotic disease.* Cambridge, Massachusetts; London, England: Harvard University Press, 1980.

4 Pooling Project Research Group. Relationship of blood pressure, relative weight and ECG abnormalities to incidence of major coronary events: final report. *J Chronic Dis* 1978;**31**:201-306.

5 Jarrett RJ, Shipley MJ, Rose G. Weight and mortality in the Whitehall study. *Br Med J* 1982;**285**:535-7.

6 Reid DD, Hamilton PJS, McCartney P, Rose G. Smoking and other risk factors for coronary heart disease in British civil servants. *Lancet* 1976;ii:79-84.

7 Rabkin SW, Mathewson FAL, Hsu P. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period. The Manitoba study. *Am J Cardiol* 1977;**39**:452-8.

8 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26 year follow-up of participants in the Framingham heart study. *Circulation* 1983;**67**:968-77.

9 Larsson B, Björntorp P, Tibblin G. The health consequences of moderate obesity. *Int J Obes* 1981;**5**:97-116.

10 Tibblin G. High blood pressure in men aged 50. A population study of men born in 1913. *Acta Med Scand* 1967;suppl 470.

11 Tibblin G. A population study of 50-year-old men. An analysis of the non-participation groups. *Acta Med Scand* 1965;**178**:453-9.

12 Cramér K, Isaksson B. An evaluation of the Theorell method for the determination of total serum cholesterol. *Scand J Clin Lab Invest* 1959;**11**:213-6.

13 Elmfeldt D, Wilhelmsen L, Tibblin G, Vedin A, Wilhelmsson CE, Bengtsson C. Registration of myocardial infarction in the city of Göteborg, Sweden. A community study. *J Chronic Dis* 1975;**28**:173-86.

14 Harmsen P, Tibblin G. A stroke register in Göteborg, Sweden. *Acta Med Scand* 1972;**191**:463-70.

15 Bradley JV. *Distribution-free statistical tests.* London: Prentice-Hall, 1968:68-86.

16 Larsson B. Obesity. A population study of men, with special reference to development and consequence for the health. Gotab, Kungälv, Sweden: University of Göteborg, 1978. PhD thesis.

17 Garrison RJ, Feinleib M, Castelli WP, McNamara PM. Cigarette smoking as a confounder of the relationship between relative weight and long-term mortality. The Framingham heart study. *JAMA* 1983;**249**:2199-203.

18 Vague J. The degree of masculine differentiation of obesities, a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *Am J Clin Nutr* 1956;**4**:20-34.

19 Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women—importance of regional adipose tissue distribution. *J Clin Invest* 1983;**72**:1150-62.

20 Landsberg L, Young IB. Fasting, feeding and regulation of the sympathetic nervous system. *N Engl J Med* 1978;**298**:1295-301.

21 Horton ES. The role of exercise in the treatment of hypertension in obesity. *Int J Obes* 1981;**5**, suppl 1:165-71.

22 Carlson LA, Boberg J, Högstedt B. Some physiological and clinical implications of lipid mobilization from adipose tissue. In: Renold AE, Cahill GF, eds. *Handbook of physiology.* Section V. Adipose tissue. Baltimore, Maryland: Williams & Wilkins Co, 1965:625-44.

(*Accepted 8 February 1984*)